REMARKS/ARUGMENTS

Upon entry of this reply, claims 1, 11, 13 and 20 will be amended, whereby claims 1-26 will remain pending. Claims 1, 11, 13 and 20 are independent claims.

By the amendments herein, the claims have been amended to even more clearly denote Applicants' invention in accordance with Applicants' originally filed disclosure and therefore the claim amendments should not be considered to raise an issue of new matter.

For example, amendments have been made to the claims to utilize the language "mixing" instead of "interaction", and this change will be discussed in the remarks presented below. Also, in conformance with Applicants' originally filed disclosure, the claims having been amended to change "inducing cellular immunity" to "inducing cytotoxic T cells" and to recite antigen inducing cytotoxic T cells. Support for these amendments appear throughout Applicants' originally filed application including page 1, first full paragraph; page 4, lines 4-24; page 6, lines 2 and 3; and page 7, last full paragraph.

Reconsideration and allowance of the application are respectfully requested.

Information Disclosure Statement

Applicants express appreciation for the inclusion with the Office Action of an initialed copy of the Form PTO-1449 submitted with the response filed May 20, 2005, whereby the Examiner's consideration of the information discussed in the response is formally of record in this application.

However, upon review of the initialed forms, Applicants again note, as previously pointed out in their response filed January 13, 2004, that the Examiner has only initialed the English language abstracts for WO98/09650 and WO92/04887 and has not initialed the Japanese documents Byotai Seiri and JP61-69801, JP63-319046, JP3-292301, JP7-97333 and JP7-206903 on Form PTO-1449 submitted with Information Disclosure Statements filed July 9, 2001 and August 8, 2003.

With respect to the above, Applicants once again respectfully submit that each of the documents contains an English abstract, is cited in a communication from a foreign office action which is written in English, and/or the documents are cited and discussed in the specification, at pages 2-3 and page 6. In particular:

WO98/09650 is accompanied by an English abstract, is cited in the International Search Report of which an English copy has been provided, and Statement and is cited and discussed in the specification beginning at page 3. Moreover, the national stage U.S. application of the international application that published as WO 98/09650 was submitted in the Supplemental Information Disclosure Statement;

WO92/04887 is accompanied by an English abstract, is cited in the International Search Report of which an English copy has been provided and the document is cited and discussed in the specification beginning at page 3;

JP 61-69801 is accompanied by an English Abstract and is cited and discussed in the specification beginning at page 3;

JP 63-319046 is accompanied by an English Abstract and is cited and discussed in the specification beginning at page 3;

JP 3-292301 is accompanied by an English Abstract and is cited and discussed in the specification beginning at page 6;

JP 7-97333 is accompanied by an English Abstract and a Patent Abstracts of Japan and is cited and discussed in the specification beginning at page 6;

JP 7-206903 is accompanied by an explanation thereof and a Patent Abstracts of Japan; and

Byotai Seiri (Pathophysiology), Vol. 6, No. 10, pp. 771-780 (1987), is accompanied by an English translation of Fig. 5 at page 776 thereof.

Still further, the initialed forms confirm the Examiner's consideration of the English abstracts, and it is respectfully requested that the crossed through documents be initialed in order that these documents will appear on the face of the issued patent along with the English abstracts. **Applicants are therefore submitting an additional Form PTO-1449 citing the crossed through documents. The Examiner is therefore respectfully requested to forward an initialed copy of the forms with the next communication from the Patent and Trademark Office.**

If the Examiner deems that any further information is necessary, the Examiner is respectfully requested to contact the undersigned by telephone to discuss the same.

Rejection Under 35 U.S.C. 112, first paragraph

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, as the Examiner asserts that the specification does not contain a written description of the claimed subject matter. This is a new matter rejection with the Examiner contending that the term "interaction" is not found in the specification.

In response to this ground of rejection, Applicants respectfully submit that one having ordinary skill in the art would understand that the claimed subject matter pending prior to the present amendment are supported by the originally filed disclosure. However, to advance prosecution of the application, the claims have been amended to utilize terminology that is explicitly in the originally filed application. Thus, the claims have been amended to recite "mixing", and attention is directed, for example, to the originally filed specification, in the last complete paragraph on page 7 wherein the term "mixing" is utilized.

In view of the above, this ground of rejection should be withdrawn.

Art Based Rejections

The following rejections are set forth in the Office Action:

(a) Claims 1-3, 6, 11, 12, 15, 18 and 20 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kohno et al., Cellular Immunology, 168, 211-219 (1996).

(b) Claims 1-24 are rejected under 35 U.S.C. 103(a) as obvious over Nestle in view of Gu et al. (hereinafter "Gu 1"), Acta Med. Nagasaki, Vol. 42, pp. 19-24 (1997)

(c) Claims 1-26 are rejected under 35 U.S.C. 103(a) as obvious over Nestle in view of Gu et al. (hereinafter "Gu 2"), Cancer Research 58, 3385-3390 (1998).

Response To Rejection Of Claims 1-3, 6, 11, 12, 15, 18 And 20 Under 35 U.S.C. 102(b) As Being Clearly Anticipated By Kohno

For at least the reasons advanced by Applicants in their previous responses, Kohno does not teach or suggest each and every feature recited in Applicants' claims,

either prior to the present amendment or the currently pending claims, whereby this ground of rejection is without appropriate basis, and should be withdrawn.

Thus, Kohno does not teach, as recited in independent claim 1, a cell capable of inducing cytotoxic T cells, said cell comprising an *in vitro* reaction product of a complex with an antigen-presenting cell, said complex formed from mixing of a hydrophobized polysaccharide and an antigen inducing cytotoxic T cells; or as recited in claim11 a method for preparing a cell capable of inducing cellular immunity comprising reacting *in vitro* a complex with an antigen-presenting cell, said complex formed from mixing of a hydrophobized polysaccharide and an antigen inducing cytotoxic T cells; or; or as recited in claim 20, an *in vitro* cell capable of inducing cellular immunity, said *in vitro* cell comprising a complex comprising a combination of a hydrophobized polysaccharide, antigen inducing cytotoxic T cells and an antigen-presenting cell.

As previously noted by Applicants, the rejection appears to be maintaining that the protein of Kohno could be both an antigen and a hydrophobizing agent. Whether or not this is an accurate statement of the disclosure of Kohno, the claims do not include such an interpretation. According to Applicants' claims and clear from Applicants' disclosure, such as Example 1, the term "complex" is directed to a conjugate, e.g., an aggregate, formed from interaction of a hydrophobized polysaccharide and an antigen. The whole cell system is obtained by reaction of a complex, i.e., a result of formation of a particle using a hydrophobized polysaccharide and an antigen, with an antigen-presenting cell. Certainly, Kohno does not disclose a complex formed from interaction of a hydrophobic polysaccharide and an antigen.

Still further, Applicants note that Kohno discloses that APC reacted with SBP-pullulan stimulates SBP-specific T cell. However, Kohno neither teaches nor suggests that the resulting cell includes cytotoxic T cells. Kohno discloses at page 212, right column, lines 17 to 15 from the bottom, that "The SBP-specific T cell lines thus established were found to be composed of only $CD4^+$ cells as determined by flow cytometric analysis.", which clearly indicates that SBP-specific T cells were $CD4^+$ cells, and not cytotoxic T cells as being CD cells as being $CD8^+$ cells.

Further, Sugi-basic protein disclosed in Kohno is an extracellularly-derived antigen and not an antigen produced by a pathologic virus and the like which is infective to human cells. Therefore, it appears that a cell activated by using Sugi-basic protein will not induce cytotoxic T cell (CTL).

Kohno therefore does not teach each any every feature of Applicants' claims, and this rejection should be withdrawn.

Moreover, to further emphasize differences between Applicants' claimed subject matter and that disclosed by Kohno, Applicants note that Kohno discloses at page 211, right column, at lines 15 to 5 from the bottom, a purpose of his research being apparently directed to a therapeutic treatment of allergic diseases such as pollen allergy by suppressing the production of a SBP specific Th2 cytokine by administration of SBP-P to activate Th1 helper T cells. This is different from the presently claimed invention which excludes a host cell such as a cancer cell or a virus-infected cell by activating an antigen-specific CTL. The antigen inducing cytotoxic T cells of the presently claimed invention are not structured to provide therapeutic effect on allergic diseases which are targets of the Kohno's method, an Kohno does not teach cells according to Applicants'

cells that include an *in vitro* cell capable of inducing cellular immunity, with the *in vitro* cell comprising a complex comprising a combination of a hydrophobized polysaccharide, antigen inducing cytotoxic T cells and an antigen-presenting cell.

Therefore, Applicants once again submit that this ground of rejection should be withdrawn.

Response To Rejections Under 35 U.S.C. 103(a) As Obvious Over Nestle In View Of Gu 1 or Gu 2

In these grounds of rejection, the rejections contend that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a product for, and perform a method for, inducing cellular immunity comprising isolating a DC APC, reacting said APC with a tumor antigen, and returning the resulting cell to the living body by parenteral administration, as taught by Nestle. The rejection utilizing Gu 1 concludes that one of ordinary skill in the art at the time of the invention would have been motivated to employ the cholesterol bearing mannan polysaccharide complexed to an ErbB-2 antigen of Gu 1 given the teachings of the reference that the ErbB-2– antigen is overexpressed in a wide range of human adenocarcnomas (and would thus provide an obvious target for immunotherapy) and that the use of the cholesterol bearing mannan polysaccharide facilitates the entry of the antigen into the MHC Class I pathway for presentation by APCs. The rejection utilizing Gu 2 concludes that one of ordinary skill in the art at the time of the invention would have been motivated to employ the cholesterol bearing mannan or pullulan polysaccharide complexed to HER2 antigen of Gu 2 given the teachings of the reference that the hydrophobed

polysaccharide-antigen complex facilitates the entry of the antigen into an APC through a carbohydrate-recognizing receptor such as DEC-205, and entry into the cytosol (for transport to MHC Claim I) after phagocytosis, for superior, antigen presentation and cellular immunity.

In response, Applicants respectfully submit that Nestle relates to an immunotherapy by using cells, however, the method of Nestle merely uses APC cells, which are isolated from a patient, for delivery of an antigen. The technical feature of Nestle is disclosed at page 328, right column, lines 12 to 15, wherein pulsing with a cocktail of peptides known to be recognized by cytotoxic T lymphocytes is discussed. This technique is similar to that disclosed for attempt (3) in Applicants' specification, at page 2, beginning at line 10, with specific discussion beginning at line 15 and continuing through the next paragraph.

Nestle also discloses at page 28, right column, beginning at line 15, that tumor lysate was used instead of peptide as source of tumor antigen in four patients. The method, which is specifically mentioned as using tumor cell lysate as a source of tumor antigen, is only applied to a patient who inherently does not express HLA-A1 or HLA-A2 (see, Nestle, page 332, left column, in the item "Pulsing of *in vitro* generated DCs").

Therefore, from this disclosure it is apparent that Nestle conducted their research to achieve the delivery of a peptide, which is chemically synthesized or is already generated in a tumor lysate, by binding to any one of HLA molecule (i.e., class I molecule) on the surface of DCs.

Gu 1 and GU 2 disclose induction of DC8 together with CTLs from cholesteryl group-bearing pullulan or cholesterol group-bearing mannan. However, the method of

Gu 1 or Gu 2 is directed to expression of variety of antigen peptides, which are processed through MHC class I pathway, simultaneously on APC cells, which is distinguishable from a mere delivery of antigen peptides.

As explained above, although the inventions of Nestle, Gu 1 and Gu 2 relate to cytotoxic T cell, the intended pathway for the antigen in APC cells of Nestle is different from that of Gu 1 and Gu 2, and moreover, the intended mechanism of expression of the antigen on the surface of APC cells by Nestle is also different from that of Gu 1 or Gu 2. Therefore, one of ordinary skill in the art would not have been motivated to combine the disclosure of Nestle which merely intends to use the APC for the delivery of the antigen peptide, with the disclosure of either of Gu 1 or Gu 2 which intends to simultaneously express a variety of antigen peptide processed by MHC class I pathway on the surface of the APC cells to achieve the present invention.

Further, while Appellants' invention does establish unexpected results, it is pointed out that a requirement for synergism or synergistic effect is nowhere found in the patent statute. When present synergism may point toward nonobviousness, but its absence has no place in evaluating the evidence on obviousness. Stratoflex Inc. v. Aeroquip Corp., 213 U.S.P.Q. 871, 880 (Fed. Cir. 1983). In other words, in order for a rejection to be proper, the rejection must fully and completely set forth the state of the art, analyze each of applicants' pending claims, apply the prior art to each of applicants' pending claims explaining any differences between the claimed invention and the prior art, and thoroughly explain how the prior art is being modified to arrive at the claimed invention by utilizing motivation supplied by the prior art and not gleaned only from Applicants' disclosure.

For the reasons set forth above, Applicants respectfully submit that a *prima facie* case of obviousness has not been established, and the rejections of record should be withdrawn. Thus, whether or not unexpected results are present, which Applicants submit are present, Applicants' claimed subject matter is patentable over the prior art of record.

Regarding unexpected results, Applicants note that the Office Action is apparently requiring that Applicants compare their invention to their own invention. Of course, this is not the standard. As stated in MPEP 716.02(e), under heading III, Rev. 3, August 2005, "Although evidence of unexpected results must compare the claimed invention with the closest prior art, applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art." This would in effect be requiring applicant to compare the results of the invention with the results of the invention.

The Examiner is reminded that in order to further denote the advantages of Applicants' claimed products and methods over a combination of Nestle and Gu 1, Applicants pointed to information regarding the subject matter as disclosed in Gu 1. In particular, Applicants made reference to Wang et al., International Journal of Oncology 14, 695-701, 1999 and Ikuta et al., Blood, 15 May 2002, Volume 99, No. 10. In particular, Applicants' invention comprises the inclusion of an antigen-presenting cell with a complex comprising a hydrophobized polysaccharide and an antigen. As can be seen in Fig. 1 of Wang et al. (which is similar to Fig. 5 of Gu 1 for CHM-HER2 instead of CHP-HER2 in Wang et al.) as compared to Fig. 5 of Wang et al., dentritic cell pretreated CHP-CAB complexes provide tumor suppression even after 10 days whereas unpretreated CHP-CAB complexes show tumor suppression through 3 days. This is further evidence

of the structural and advantageous differences between Applicants' claimed subject matter and that disclosed by either Gu 1 or Gu 2.

Expanding upon the above, Figs. 1 and 5 of Wang et al. are being compared, and it is merely being noted that Fig. 1 of Wang et al. is similar to Fig. 5 of Gu 1 to assist the Examiner's understanding of unexpected results associated with Applicants' invention over the prior art utilized in the rejections.

The rejection utilizing Gu 1 also contends that it is inappropriate to assert superior or unexpected results not disclosed in the specification in an attempt to overcome an art rejection. However, in contrast to this assertion, Applicants' originally filed disclosure provides a showing of unexpected results in contrasting Applicants' invention with prior techniques, such as on pages 2 and 3 of the specification. Moreover, Applicants have provided Examples showing the superior results associated with Applicants' invention.

Accordingly, Applicants respectfully submit that the record is clear that Nestle does not teach or suggest any use of a hydrophobized polysaccharide; does not teach or suggest any use of a complex of a hydrophobized polysaccharide and an antigen; and does not teach or suggest any use of any type of combination of an antigen-presenting cell, a hydrophobic polysaccharide and an antigen. The record is also clear that there is no motivation to combine Gu 1 or Gu 2 with Nestle.

Applicants once again also bring to the Examiner's attention that the hydrophobized polysaccharide according to the present invention can form a complex with a tumor antigen, whereas a polysaccharide in the prior art cannot form a complex with a tumor antigen. Thus, for this additional reason, the presently claimed invention would not have been obvious to one skilled in the art.

Therefore, Applicants respectfully submit that this rejection is without appropriate basis, and should be withdrawn.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow each of the pending claims.

Applicants therefore respectfully request that an early indication of allowance of the application be indicated by the mailing of the Notices of Allowance and Allowability.

Should the Examiner have any questions regarding this application, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,
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